Decision Summary

Medicare Administrative Contractors acting within their respective jurisdictions may determine coverage of adult liver transplantation for the following malignancies: (1) extrahepatic unresectable cholangiocarcinoma (CCA) (2) liver metastases due to a neuroendocrine tumor (NET) and (3) hemangioendothelioma (HAE).

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Decision Memo

TO: Administrative File: Liver Transplantation for Patients with Malignancies CAG-00091R
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SUBJECT: National Coverage Determination (Reconsideration) Liver Transplantation for Patients with Malignancies
DATE: June 21, 2012

I. Decision:

Medicare Administrative Contractors acting within their respective jurisdictions may determine coverage of adult liver transplantation for the following malignancies: (1) extrahepatic unresectable cholangiocarcinoma (CCA) (2) liver metastases due to a neuroendocrine tumor (NET) and (3) hemangioendothelioma (HAE).

II. Background

The scope of this review was limited to consideration of coverage of liver transplantation for three types of malignancies: cholangiocarcinoma (CCA), liver metastases due to a neuroendocrine tumor (NET), and hemangioendothelioma (HAE).

Throughout this document common acronyms are used. Please find below a list of these acronyms and corresponding terminology:

AASLD American Association for the Study of Liver Diseases
CCA—Cholangiocarcinoma
EBRT External beam radiotherapy
ESLD End Stage Liver Disease
HAE /EH/ HEHE/ HEH /HE Hemangioendothelioma or Epithelioid Hemangioendothelioma or Hepatic Epithelioid Hemangioendothelioma
HCC Hepatocellular carcinoma
HRSA Health Resources and Services Administration
HB Hepatoblastoma
LT/LTx Liver transplantation
LRx Liver resection
MELD Model for End Stage Liver Disease
NCCN National Comprehensive Cancer Network
NET Neuroendocrine tumor
NLMs Neuroendocrine Liver Metastases
OPTN Organ Procurement and Transplant Network

We also list some technical terms for the convenience of the reader.

In situ – in position
Orthotopic – in the usual position

A. Malignancies of the Liver

According to the NCCN (2012), hepatobiliary cancers are highly lethal and include a spectrum of invasive carcinomas arising in the liver (hepatocellular carcinoma [HCC]), bile ducts (intrahepatic and extrahepatic cholangiocarcinoma) and gall bladder (collectively known as biliary tract cancers). In the United States an estimated 26,190 cases with liver or intrahepatic bile duct cancer and 9,250 cases of gallbladder cancer or other biliary tract cancers will be diagnosed. For 2011, they will result in approximately 19,590 deaths from liver or intrahepatic bile duct cancer, and 3,300 deaths due to gallbladder cancer or other biliary tract cancer (NCCN, 2012). Based on February 17, 2012 data from OPTN, patients with HCC, the most common of primary liver malignancies, accounted for 363 of 16,904 persons on the liver transplant waiting list in 2011; this demonstrates the relative rarity of these malignancies in the transplant population. Based on March 5, 2012 data from OPTN, in 2010, 1361 out of 6291 total liver transplants performed were related to some type of malignancy. While HCC accounts for the vast majority of primary hepatic cancers, there are a number of non-HCC malignancies for which liver transplantation may be considered as treatment.

1. <u>Cholangiocarcinoma (CCA)</u>

CCA is a cancer of the bile ducts that is often associated with pre-existing primary sclerosing cholangitis. Although it is a rare malignancy with a reported prevalence of 1.2 per 100,000 (Heimbach, 2004), it accounts for 10-15% of all hepatobiliary tumors in the US. The NCCN Guideline (2012) states that primary cholangiocarcinoma remains the most common of non-HCC malignancies. Based on OPTN data, CCA accounted for only 302 liver transplants from 2001 to 2010. CCA is described as either intrahepatic (within the liver) or extrahepatic (outside the liver). The majority of CCA (75% to 94%) is extrahepatic (Heimbach, 2004). The mortality rate for untreated CCA of either type is quite high and ranges from 50% to 70% within 12 months (Heimbach, 2004).

2. <u>Neuroendocrine tumors (NETs)</u>

Neuroendocrine cells are found throughout the body. They produce hormones and have a variety of important functions. Neuroendocrine tumors are very rare; the reported incidence is 1-2 cases per 100,000 per year (Blonski, 2005) to 5.25 cases per 100,000 per year (NCCN, 2012). According to Chan, NETs are classified as either well-differentiated (low grade [Grade 1] or intermediate grade [Grade 2]) or poorly-differentiated (high grade [Grade 3]) (Chan, 2011). Well-differentiated NETs have traditionally been called carcinoid tumors or pancreatic (neuro) endocrine tumors. Poorly-differentiated NETs have traditionally been referred to as small cell carcinoma or large cell neuroendocrine carcinoma. The well-differentiated NETs typically have a benign clinical course while the poorly-differentiated NETs have an aggressive clinical course (Chan, 2011).

The clinical presentation for patients with NETs is highly variable due to the variable location and hormone production of the primary tumor and the propensity of the tumor to metastasize. Some patients stay asymptomatic for years while other patients experience symptoms due to tumor bulk and/or the excessive secretion of hormones. The specific hormone(s) secreted by a functioning tumor will determine the constellation of symptoms and signs that a patient can experience. For example, the hormones produced by some carcinoid tumors can cause a specific constellation of symptoms and signs, such as facial flushing, wheezing, and heart disease, called the carcinoid syndrome (Chan, 2011). The hormones released by a pheochromocytoma can lead to excessively elevated blood pressure. A type of pancreatic endocrine tumor called an insulinoma can lead to a dangerously low blood sugar level.

NETs in the liver are of metastatic origin. The primary origin can be any of a number of locations (e.g., the small bowel or the pancreas). The most common NET causing liver metastases is carcinoid. Metastatic disease in the liver is rarely solitary and only a small number of patients have lesions that at the time of diagnosis are sufficiently localized to allow curative resection. NETs tend to recur, and in some patients metastases may develop many years after resection of the primary tumor. Principal treatment options include medical therapy aimed at reducing tumor size and inhibiting hormone secretion, and invasive therapies such as intra-arterial infusion of cytotoxic drugs, hepatic artery embolization, or irradiation and surgical resection or transplantation (Grossman and Millis, 2010).

The prognosis for patients with NETs is also highly variable depending on the site of origin of the tumor and degree of tumor aggressiveness. According to a review by Harring and colleagues (2011), NETs that invade the liver (neuroendocrine liver metastases [NLMs]) are associated with significant morbidity and mortality and consequently have a particularly poor prognosis compared to patients with NETs without NLMs. The authors noted that the 5-year survival rate for patients with NLMs who are receiving only supportive care is 0-20%. Half to almost all patients with NETs have NLMs upon diagnosis (Harring, 2011).

3. Hemangioendothelioma (HAE) or (EH) or (HE) or (HEHE) or (HEH)

Hepatic epithelioid hemangioendothelioma is an extremely rare, low-grade malignant neoplasm of vascular origin that originates in the vascular endothelial cells of the liver. In Hertl and Cosimi (2005), the authors stated that primary malignant HAE has an incidence of < 0.1 per 100,000 people. The clinical presentation of this disease is highly variable, i.e., some patients present with hepatic failure while other patients are asymptomatic (Mehrabi, 2006). The cancer can occur as multiple tumor nodules throughout one or both lobes of the liver or as diffuse tumor throughout the liver. The majority of patients have tumors in the lobes of the liver however extrahepatic disease may occur as well.

Patients can present with various symptoms including abdominal discomfort/pain, weight loss, weakness and fatigue. Because HAE has a widely unpredictable course and prognosis, treatment modalities are not standardized. Partial hepatectomy, chemotherapy, and radiotherapy have all been used. The wide variability in natural history of the disease limits assessment of treatment efficacy. In current best estimates, twenty percent of patients die within the first 2 years after presentation, whereas 20 percent have extended survival for 5 to 28 years, irrespective of treatment (Mehrabi, 2006).

B. Treatment for Malignancies of the Liver

Orthotopic liver transplantation (OLT), also known as liver transplantation, which is *in situ* replacement of a patient's liver with a donor liver, has become the definitive therapy for patients with end stage liver disease due to a variety of causes. However, the role of transplantation in the treatment of patients with preexisting malignancies is controversial. Included in this group are patients with primary and metastatic liver tumors, and those with a known history of extrahepatic malignancies. A number of studies have suggested that the high risk of tumor recurrence (due to residual disease and the effects of immunosuppression) in these patients may not justify OLT. On the other hand, despite its many potential short and long-term complications, OLT may offer the only chance of cure for some patients while providing meaningful palliation of symptoms for others. Advances in transplantation surgical techniques and immunosuppressive drugs have resulted in increased survival rates. Currently, 10 to 20 % of liver transplanted patients are re-transplanted with a success rate of greater than 50% (Aetna Policy Bulletin, 2011).

Liver transplantation has been an integral component of treatment regimens for HCC. In addition, more recently it has been concluded that "liver transplantation is an integral component of treatment regimens for specific non hepatocellular malignancies. In appropriately selected patients suffering from CCA, NETs, HB, or HAE, liver transplantation provides the best chance for cure or survival" (Grossman and Millis, 2010).

"The role of OLT in the therapy of hepatic malignancies has evolved dramatically over the last two decades. Despite the limited successor early trials involving OLT for patients with primary liver malignancies, novel chemotherapy regimens combined with appropriate patient selection have led to the widespread acceptance of OLT as effective treatment for HCC. Presently, the indications for OLT in patients with HCC are expanding, and liver transplantation is becoming an essential treatment component for less common hepatic tumors" (Grossman and Millis, 2010).

"OLT is currently incorporated into the treatment regimens for specific nonhepatocellular malignancies. For patients suffering from early-stage, unresectable hilar cholangiocarcinoma, OLT preceded by neoadjuvant radiotherapy has the potential to readily achieve a tumor-free margin, accomplish a radical resection, and treat underlying primary sclerosing cholangitis when present. In highly selected stage I and II patients with CCA, the 5-year survival rate is 80%. As additional data are accrued, OLT with neoadjuvant chemoradiation may become a viable alternative to resection for patients with localized, node-negative hilar CCA. Hepatic involvements from neuroendocrine tumors can be treated with OLT when metastases are unresectable or for palliation of medically uncontrollable symptoms. Five-year survival rates as high as 90% have been reported, and the Ki67 labeling index can be used to predict outcomes after OLT. Hepatic epithelioid hemangioendothelioma is a rare tumor of vascular origin. The data from single-institution series are limited, but compiled reviews have reported 1- and 10-year survival rates of 96% and 72%, respectively. Fibrolamellar hepatocellular carcinoma is a distinct liver malignancy best treated by surgical resection. However, there is an increasing amount of data supporting OLT when resection is contraindicated. In the treatment of either primary or metastatic hepatic sarcomas, unacceptable survival and recurrence rates currently prohibit the use of OLT" (Grossman and Millis, 2010).

1. Treatment for Cholangiocarcinoma (CCA)

According to Becker and colleagues (2008), results of nonsurgical treatments have been disappointing; the majority of patients survive less than 1 year upon diagnosis. If complete resection is performed, the 5-year patient survival rate has been between 27 and 48%. However, patient age, tumor location, distant disease, and/or underlying liver disease often lead to a determination of unresectable tumor. Becker also stated that in "selected cases of cholangiocarcinoma that are early-stage, but anatomically not resectable, orthotopic liver transplantation (OLT) has been investigated as a treatment modality."

Early experience with liver transplantation for unresectable CCA was associated with 5-year survival rates ranging from 18 to 25% (Becker, 2008). This compares to a median survival after treatment of unresectable CCA with radiation therapy of 9-12 months (Heimbach, 2006). However, according to Becker and colleagues "more recent single-center reports indicated that 5-year patient survivals of over 80% can be achieved when liver transplantation is combined with neoadjuvant radiation and chemotherapy in patients with early-stage disease (stage I/II)."

The OPTN Guidelines describe the allocation of livers for Transplant Candidates with Cholangiocarcinoma (CCA). Please refer to: http://optn.transplant.hrsa.gov/policiesAndBylaws/policies.asp

2. Treatment for NETs

According to a 2010 review by Grossman and Millis, symptom control and an improved quality and length of life can be achieved for patients with NLMs by using medical therapies such as radiofrequency ablation, hepatic artery embolization, hepatic artery chemoembolization, selective internal radiation therapy, chemotherapy and immunotherapy to decrease the tumor size and block the hormonal effects. These authors state that resection of the NLMs should be reserved for cases where 80% to 90% of the tumor can be removed. In a review by Harring and colleagues (2011), however, surgery is noted to be the primary treatment for NLMs because it has consistently shown better outcomes compared to nonsurgical treatments. The 5-year survival rate for resection ranges from 60% to almost 80% in the literature with a mortality rate of less than 5%. For this reason, aggressive surgery is considered to prolong survival and provide the best way to control symptoms. Harring and colleagues further stated that additional analyses have found that a subset of these patients those with poorly-differentiated NET have a significantly worse prognosis (median survival is 6 months). Tumor size, number and location also impact the patient survival rate after liver resection. In fact, only 10% to 20% of patients are found to have resectable disease upon diagnosis due to extensive tumor burden, a diffuse pattern of tumor and/or tumor in difficult-to-remove locations (Harring, 2011). Liver transplantation has been performed in patients with unresectable NLMs; it is also performed to palliate medically-uncontrollable symptoms (Grossman and Millis, 2010).

3. Treatment for HAE

In Lerut (2007), the authors stated that the course of treatment for HAE is "far from standardized mainly due to its rarity and the inability to predict its behavior and therefore the prognosis." Treatment options include liver resection, liver transplantation, chemotherapy, radiation therapy and immunotherapy. Liver resection is the treatment of choice; a 75% 5-year survival rate has been reported; however, less than 10% of patients are candidates for liver resection due to a predominantly multifocal or diffuse nature of the tumor (Rodriguez, 2008; Grossman and Millis, 2010).

Organ Allocation through OPTN

Section 1138(a) (1) (B) of the Social Security Act (the Act) requires all Medicare transplant facilities to be members of and abide by the rules of the Organ Procurement and Transplantation Network (OPTN). See also, 42 C.F.R. section 482.45(b). The OPTN contract is awarded competitively by the Department of Health and Human Services (DHHS) through the Health Resources and Services Administration (HRSA) in a 3-5 year cycle. The OPTN contractor assists the OPTN (whose membership represents stakeholders in the transplant community) in developing allocation policies related to transplantation consistent with applicable regulations. The policies can be found at: http://optn.transplant.hrsa.gov/policiesAndBylaws/policies.asp.

The HRSA regulation at 42 CFR part 121 describes general requirements for organ allocation policies developed by the OPTN to ensure the proper allocation of organs based on sound medical judgment and to achieve the best use of donated organs. Allocation policies should be "designed to avoid wasting organs, to avoid futile transplants, to promote patient access to transplantation, and to promote the efficient management of organ placement," among other factors. 42 CFR 121.8(a).

http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?type=simple;c=ecfr;cc=ecfr;sid=1c3ff1d7b46fe69dc4d4fda4c2f9ba62;idno=42;region=DIV1;q1=121;rgn=div5;view=text;node=42%3A1.0.1.11.78#42:1.0.1.11.78.0.39.8.

MELD Score

The Model for End-stage Liver Disease (MELD) scoring system is used to determine mortality risk for patients with end-stage liver disease (ESLD). Specifically, its purpose is to enable physicians to apply their consensus medical judgment for the benefit of liver transplant candidates as a group. Each candidate is assigned a status code or probability of death derived from a mortality risk score corresponding to the degree of medical urgency as described in the OPTN policy. Candidates with the highest number of points receive the highest priority for transplant. CCA patients have the potential for exception (additional) points which can elevate them on the waiting list. There are five MELD categories for adult patients: Status 1, Status 2A, Status 2B, Status 3 and Status 7. Patients listed as Status 1 have the highest priority for donor organs and those with Status 3 have the lowest priority. Status 7 represents a temporarily inactive status.

Conditions of Participation for Transplant Centers

On March 30, 2007, CMS published the Requirements for Approval and Re-Approval of Transplant Centers to Perform Organ Transplants Final Rule, which was effective on June 28, 2007. That final rule established the Conditions of Participation (CoPs) (42 CFR 482.68- 42 CFR 482.104), which requires a new certification of approval to perform transplant services after an onsite survey. The requirements in these CoPs include, but are not limited to the following. A transplant center must: (1) be a member of the OPTN; (2) notify CMS of any significant changes related to the center's transplant program or changes that could affect its compliance with the CoPs; (3) meet specific data submission, clinical experience and outcome requirements for both initial approval and re-approval; (4) use written patient selection criteria; (5) have written patient management policies performed by a multidisciplinary team for the transplant and discharge phases of transplantation; and (6) develop, implement, and maintain a written, comprehensive, data-driven quality assessment and performance improvement (QAPI) program. Transplant center approval is determined by CMS.

More detailed information can be accessed from: http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&sid=48557ceda175e8b35412757d055fa1f9&rgn=div5&view=text&node=42:5.0.1.1.1&idno=42#42:5.0.1.1.1.5.4.5.

III. History of Medicare Coverage

In 2001, CMS released a National Coverage Determination (NCD) on Liver Transplantation for Malignancies which provides that liver transplantation is reasonable and necessary for HCC. Specifically, the NCD provides Medicare coverage for adult liver transplantation for HCC when the following conditions are met:

- The patient is not a candidate for subtotal liver resection;
- The patient's tumor(s) is less than or equal to 5 cm in diameter;
- There is no macrovascular involvement;
- There is no identifiable extrahepatic spread of tumor to surrounding lymph nodes, lungs, abdominal organs or bone; and
- The transplant is furnished in a facility which is approved by CMS as meeting institutional coverage criteria for liver transplants (See 65 FR 15006).

In 2002, CMS released a decision memorandum and NCD on Liver Transplantation for Malignancies other than Hepatocellular Carcinoma, in which CMS delineated the reasons for continuing Medicare non-coverage of liver transplantation for malignancies other than HCC. Specifically, our determination was based on the review of non-HCC malignancies and treatment options available at that time, and a technology assessment for non-HCC malignancies. CMS determined that the evidence was not adequate to conclude that liver transplantation in patients with non-HCC malignancies was clinically effective. Therefore, CMS determined that the item or service was experimental and CMS continued its national non-coverage of liver transplantation for malignancies other than HCC:

http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=70&ncdver=2&bc=AAAAgAAAAAAA&

Previous analysis had indicated that long-term survival for liver transplants performed on patients with malignancies was significantly lower than for other indications. Currently, adult liver transplantation for malignancies other than HCC remains noncovered.

Benefit Category

For an item or service to be covered by the Medicare program, it must fall within one of the statutorily defined benefit categories outlined in the Social Security Act. Liver transplantation falls under the benefit categories set forth in section §1861(b) (3) (inpatient hospital services), a part A benefit, under §1812(a) (1), and §1861(s) (1) (physician services), a part B benefit. This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

B. This Consideration

CMS opened this analysis to review new evidence on the impact on health outcomes of liver transplantation in beneficiaries who have malignancies.

This analysis was limited to evaluating evidence for liver transplantation in malignancies for patients with 1) CCA, 2) liver metastases due to a NET, or 3) HAE. We did not review other malignancies in this reconsideration.

IV. Timeline of Recent Activities

October 14, 2011	CMS initiates a reconsideration of the NCD for liver transplantation for malignancies.
November 13, 2011	The initial 30 day public comment period closes.
March 29, 2012	The proposed decision memorandum is posted; second 30-day public comment period begins.
April 28, 2012	The second 30-day public comment period closes.

V. FDA Status

We are not aware of any FDA regulatory determinations on this surgical procedure.

VI. General Methodological Principles

When making national coverage determinations under 1862(a)(1)(A) of the Social Security Act, CMS generally evaluates relevant clinical evidence to determine whether or not the evidence is sufficient to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that the agency utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A.

Public comment sometimes cites the published clinical evidence and gives CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

VII. Evidence

A. Introduction

In this analysis, we considered evidence for liver transplantation for these malignancies: CCA, NET, or HAE. Clinical trials in cancer often report a variety of outcomes that differ in their persuasiveness as evidence. As we have stated in Appendix A of this document,

> CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses.

Thus, in reviewing the evidence for this decision we were particularly attentive to reports of changes in those clinical outcomes experienced by patients.

Both patients and providers are interested in quantifying prognosis as an outcome. Though death can be the final endpoint (or expressed in terms of survival) with the interval to death as that of interest, other endpoints can be examined such as interval to disease recurrence, time to functional impairment, or changes in the patient's quality of life (Gordis, 2000). One very common approach to expressing prognosis is observed survival using the Kaplan-Meier method. Patients enter into the analysis as they are enrolled in treatment and remain in the analysis until they meet the analysis endpoint or drop-out for some reason (known as censoring). All information is used on an interval basis (such as 1-year survival) to describe the survival experience, regardless of length of time in the analysis. This conceptual framework accounts for censored observations (i.e., dropouts) and allows for the maximal use of data. There are two important methodologic assumptions with this type of analysis (Gordis, 2000). The first is that there is no change over time in the treatment effectiveness (no improvements in treatment over time) and with that no change in survivorship based on when a patient enrolled in the study. This may not hold in that treatments generally change over time. The second is that the patients who drop out of the analysis have the same survival characteristic as those who do not drop out, which is difficult to prove and represents selection bias. With increasing study drop-outs, confidence in the analysis conclusions is weakened.

B. Literature Search

CMS performed a literature search using PubMed on December 1, 2011 with the search terms "Cholangiocarcinoma," and "Liver Transplantation" for the cholangiocarcinoma literature search; "Neuroendocrine Tumor," and "Liver Transplantation" for the neuroendocrine tumor literature search; and "Hemangioendothelioma," and "Liver Transplantation" for the hemangioendothelioma literature search. The following limitations were applied: Humans, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, and Multicenter Study as well as English, All Adult: 19+ years and Publication Date from 2001/01/01 to 2011/12/01. A second literature search was performed for each malignancy on May 9, 2012 using the same search terms except the Publication Date was from 2011/12/01 to 2012/05/09. This second search did not retrieve any new articles.

C. Discussion of Evidence Reviewed

1. Questions:

1. Is the evidence adequate to conclude that liver transplantation improves health outcomes of Medicare beneficiaries with cholangiocarcinoma?
2. Is the evidence adequate to conclude that liver transplantation improves health outcomes of Medicare beneficiaries with liver metastases due to a neuroendocrine tumor?
3. Is the evidence adequate to conclude that liver transplantation improves health outcomes of Medicare beneficiaries with hemangioendothelioma?

2. External Technology Assessments (TA)

An external TA was not commissioned. No external TA was found upon a search of the literature or a search of the Internet, other than the TA noted in the NCD.

3. Internal technology assessment

Cholangiocarcinoma

Five articles were identified for further review during the literature search. Three articles (Hassoun, 2002; Heimbach, 2004; Rea, 2005) were earlier publications of the patients reported in Heimbach, 2006, which is reviewed below. The second article reviewed below (Becker, 2008) presented an analysis of OPTN data, of which the patients reported in Heimbach may be a subset. Two e-publications (Murad, Kim, Harnois, 2012; Murad, Kim, Therneau, 2012) reporting outcomes of patients with cholangiocarcinoma who received a liver transplantation were submitted during the final public comment period and included in this internal technology assessment.

Heimbach JK, et al. Predictors of disease recurrence following neoadjuvant chemoradiotherapy and liver transplantation for unresectable perihilar cholangiocarcinoma. Transplantation 2006;82:1703-1707.

Heimbach and colleagues reported the results of a retrospective analysis of 65 patients with confirmed stage I or stage II unresectable hilar CCA who underwent liver transplantation at the Mayo Clinic Rochester between January, 1993 and January, 2006. The goal of the analysis was to "identify clinicopathological predictors of disease recurrence after transplantation in patients who have completed neoadjuvant therapy and subsequently underwent OLT." A definition of "unresectable" was not given except to note that "all patients with de novo CCA were evaluated for resectability by an experienced hepatobiliary surgeon." The exclusion criteria included:

- Prior chemotherapy or radiotherapy
- Uncontrolled infection
- Previous malignancy within five years
- Medical conditions precluding transplantation (details or examples not provided)
- Extrahepatic disease (including regional lymph node involvement)
- Operative biopsy or attempted resection of the tumor
- A discreet mass with a clear radial diameter >3 cm on cross-sectional imaging
- Until the year 2000, the presence of hilar disease that extends below the cystic duct
- A positive staging laparotomy (details not provided)

The treatment regimen consisted of external beam radiotherapy, brachytherapy and a continuous intravenous infusion of 5-fluorouracil and oral capecitabine followed by a staging laparotomy and finally liver transplantation.

Patients were seen "at four months and then annually after transplantation, or if indicated. Routine laboratory tests, CA 19-9 level, liver ultrasonography and chest and abdominal computed tomography (CT) were obtained at each follow-up visit." The authors noted that "[S]tatistical analysis of survival and recurrence rates was performed using the Kaplan-Meier method. Determination of risk factors predictive of disease recurrence was made with a Cox regression analysis. P values less than 0.05 were considered significant." There was no control group.

The authors stated that "106 patients began the treatment protocol. Eleven patients had evidence of disease spread or died from complications prior to completion of adjuvant chemoradiotherapy. There were 94 patients who underwent staging laparotomy, 18 (19%) of those had disease spread precluding transplantation. At the time of analysis, there were eight patients awaiting transplantation and 65 patients who had undergone OLT at our institution."

The median age of the patients was 49 years (range, 22 - 66); only eight patients were older than 60 years. Fourteen (21%) patients had a mass observable on imaging. The authors stated that "[F]our patients died from perioperative complications after OLT; none had evidence of recurrent disease at autopsy. Eleven patients (17%) developed recurrent CCA after OLT and eight have died as a result (Fig 2). The mean onset of recurrence was 29 months, with a median of 22 months and a range of seven to 65 months from transplantation. The sites of recurrence were distant metastases in eight and regional metastases in three. The mean follow-up was 32 months (2.7 years), with a median of 18 months and a range of 2 days to 13 years."

An increased age at transplantation, prior cholecystectomy and a discreet radial mass seen on cross-sectional imaging (up to 3 cm) were factors associated with recurrence. The authors stated that "an increased risk of recurrence began to be evident at approximately age 45, as only 1 of 24 patients age 45 or less had recurrence while 10 of 42 patients (24%) age > 45 had recurrence. Kaplan-Meier analysis also demonstrated a separation between groups based upon age ≤ 45 versus age > 45." Quality of life outcomes were not reported.

The authors stated that the "intent of the protocol was to decrease local recurrence and tumor dissemination at the time of transplantation. As previously reported, outcomes utilizing the combined chemoradiotherapy and liver transplantation are superior to liver transplantation alone or resection (15%). Patients survival of 91% at one year and 76% at five years is similar to that achieved for OLT other standard indications for OLT such as hepatocellular carcinoma or hepatitis C virus. However the toxicity of the treatment is significant. Despite an aggressive pretreatment protocol, 11 of 65 (17%) still develop recurrent disease."

The authors noted that the "University of Nebraska developed a similar approach to the treatment of unresectable hilar cholangiocarcinoma which employs brachytherapy at a higher dose (6000 cGy) without external beam radiotherapy (23%). Five of the 11 patients were alive and disease-free 2.8 to 14.5 years after transplantation, with two of the six deaths due to tumor recurrence. Although there were more deaths attributable to perioperative complications, the tumor response was similar to our experience."

The authors concluded that "neoadjuvant chemoradiotherapy with subsequent OLT achieves excellent results for patients with localized hilar CCA. Older patients and those with larger, more aggressive tumors are at a higher risk of disease recurrence." The authors then noted that "[T]hese factors may warrant consideration when enrolling patients or in guiding organ allocation policy."

Becker NS, et al. Outcomes analysis for 280 patients with cholangiocarcinoma treated with liver transplantation over an 18-year period. Journal of Gastrointestinal Surgery 2008;12:117-122.

Becker performed a retrospective analysis of the OPTN database. Of the 71,224 liver transplants from 1987 to 2005, 280 were in patients with a diagnosis of CCA; the authors did not report more detailed information about these patients' diagnosis, e.g., early vs. late stage or extent of extrahepatic disease. However, they did note that 177 patients were transplanted before the implementation of the MELD scoring system. Details regarding the specific treatment regimen received by each patient were not reported. The goal of the analysis was to examine overall trends in outcomes following OLT for cholangiocarcinoma.

Patient survival rates were determined using Kaplan-Meier curves. The prognostic value of patient age, race, gender, indication for transplant, pretransplant clinical status, ABO blood group, allograft type, date of transplant, patient and allograft survivals and cause of allograft failure or death (cancer-related vs. other cause) with regards to patient survival were determined using log-rank tests. A p value of < 0.05 was considered to be statistically significant. Quality of life outcomes were not evaluated. There was no control group. The median age was 48 years (range, 18 - 73). The exact number or percentage of patients who were ≥ 65 years old was not reported.

The authors reported that "[T]welve patients died within 30 days of primary transplant, yielding a 30-day mortality rate of 4.0%. At a median patient follow-up interval of 452 days (range: 0 – 6166 days), 1- and 5-year patient survival for all 280 study patients were 74% and 38%, respectively. There were 49 actual 5-year survivors and 21 actual 10-year survivors." Regarding patient survival when examined by cause of death, the authors noted that of "the 128 patients who died more than 30 days post-OLT, the cause of death was known in 114 of these 128 cases (89%). Of these, 55 patients died from locally recurrent (19 patients) or metastatic disease (36 patients), 24 patients died from infection, 13 patients died from allograft failure, and 22 patients died from other causes. Patients who died from recurrent disease had 1- and 5-year survival rates of 76% and 17%, respectively, with a median survival of 601 days compared with 1-year, 5-year, and median survivals of 44%, 3%, and 322 days for those who died from non-cancer causes ($p < 0.005$)."

In the analysis to determine the prognostic value of multiple clinical variables, the authors noted that "[A]ge, race, gender, and blood group had no impact on patient survivals. Allograft type and status 1 listing also had no impact on survival. Clinical variables that were significant predictors of worse survival included inpatients hospitalization prior to transplant ($p = 0.006$), ICU admission prior to transplant ($p < 0.001$), serum creatinine ≥ 1.5 mg/dL ($p < 0.001$), and serum bilirubin ≥ 2.0 mg/dL ($p = 0.015$)."

The authors concluded that their analysis "determined that outcomes following OLT for cholangiocarcinoma have improved over time with a 5-year survival rate of 45% during the most recent era of transplantation. Compared to outcomes in similar patients treated with medical therapy alone, patients with known cholangiocarcinoma that presents at an early, but unresectable, stage appear to benefit from OLT."

Murad SD, Kim WR, Harnois DM, et al. Efficacy of neoadjuvant chemoradiation, follow by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. Gastroenterology 2012, doi: 10.1053/j.gstro.2012.04.008.

Murad and colleagues conducted a retrospective analysis of data collected during an onsite review of protocols and medical charts from 12 "large-volume transplant centers in the US." The goals of the analysis were to examine "the U.S. experience to: 1) evaluate the overall effectiveness of neoadjuvant therapy followed by LT for perihilar cholangiocarcinoma; 2) assess the impact of inter-center variance in selection and neoadjuvant therapies; and 3) determine whether the current MELD exception score is appropriate."

The authors "invited 50 large-volume adult U.S. liver transplant programs to participate if they had 1) an established protocol for transplantation for perihilar cholangiocarcinoma employing neoadjuvant therapy, and 2) transplanted three or more patients under this protocol from January 1993 to July 2010. In total 30 centers (60%) responded to the mailing; 8 (27%) did not have a protocol and had not treated anyone with neoadjuvant chemoradiotherapy and LT, 10 (33%) did have an approved protocol but had performed less than three transplants, and 12 centers (40%) fulfilled both criteria."

Inclusion criteria for the patient population consisted of "1) perihilar cholangiocarcinoma; 2) diagnosis by a malignant-appearing stricture on cholangiography with malignant endoluminal brushing/biopsy, CA 19-9 greater than 100 U/ml, mass on cross-sectional imaging and/or polysomy on Fluorescent in-Situ Hybridization (FISH); 3) unresectable disease or arising in Primary Sclerosing Cholangitis; 4) completion of neoadjuvant therapy before LT; and 5) medical suitability for transplantation. Patients with intrahepatic or distal cholangiocarcinoma were excluded." The authors defined neoadjuvant therapy as "any combination of chemotherapy, external beam radiotherapy and/or brachytherapy given prior to LT."

The definition of "dropout" was "positive staging, tumor metastasis, death or withdrawal at any time before transplantation." Recurrence was defined as "radiographic or pathologically confirmed evidence of cholangiocarcinoma post-transplantation." Survival was calculated using the Kaplan Meier method and compared using the log-rank test. There was no control group.

The 12 centers enrolled a total of 319 patients but 26 of these patients did not satisfy the inclusion/exclusion criteria for this analysis therefore only 287 patients were eligible for the analysis. Center 1 had 193 eligible patients and the remaining 11 centers had 94 eligible patients. The number of eligible patients per center for these remaining 11 centers was not reported. The name and location of each of the 12 centers were also not reported.

Seventy-one patients (25%) dropped out between 1.1 and 17.1 months (median, 4.6) after presentation. This dropout group had a statistically significant lower rate of primary sclerosing cholangitis, higher rate of mass on cross-sectional imaging, higher CA 19-9 and bilirubin and platelet levels and higher MELD score compared to the patients who remained eligible for liver transplantation. The median age of the dropout group was 52 years (range, 27 – 70) and of the remaining eligible group was 50 years (range, 17 – 69); the number of patients that were 65 years old or older in each group was not reported.

After liver transplantation, the recurrence-free survival rate was 78% (95% CI, 72 – 84), 65% (95% CI, 57 – 73) and 59% (95% CI, 49 – 69) at two, five and 10 years, respectively. The authors noted that patients "who were transplanted outside of current UNOS/OPTN criteria for MELD exception (i.e. mass > 3 cm (N = 21), metastatic disease at transplantation (N = 4), or direct tumor biopsy (n = 16)), or who had a history of previous malignancy within 5 years (n = 7) had significantly worse recurrence-free survival as compared to those with criteria (HR 2.98 (95% CI 1.79 – 4.95)."

The authors also examined the treatment effect by center and noted that despite one of the twelve centers having contributed the largest number of patients (i.e., Center 1 with 193 patients), "we found no significant difference in median follow-up (2.49 vs. 2.54; P = .91), intent-to-treat (P = .29; Figure 3e) or recurrence-free survival (P = .18; Figure 3f) between this center and all other centers (N = 94). This remained true (HR 0.82; 95% CI 0.43 – 1.54) even after correcting for differences in staging (HR 0.95; 95% CI 0.44 – 2.07), brachytherapy (HR 1.31; 95% CI 0.70 – 2.46) and selection criteria (HR 2.89; 95% CI 1.70 – 4.97) in a multivariate Cox regression model. Note that selection remained the only significant determinant of recurrence-free survival (P < .001)."

Murad and colleagues stated that in "addition to these 12, we identified at least 10 other centers with UNOS-OPTN approved protocols who are actively enrolling and treating patients. Our data serves to justify the use of scarce liver allografts for this otherwise lethal disease, as the unadjusted 5-year disease-free survival of 65% is not only similar to results from earlier single-center series but also similar to outcomes of liver transplantation for other malignant and non-malignant indications. Finally, the observed 3-month dropout rate provides justification for the use of MELD exception to expedite transplantation for this indication." The authors further note that these criteria were "found to be highly predictive of successful outcome. As a matter of fact, selection represents the only variable that acts as an independent predictor of outcome and is modifiable at the same time. By adjusting selection alone, 5-year recurrence-free survival can be maximized to 72%."

The authors identified three limitations with their analysis. "The main limitation of our study is that it is not a randomized controlled trial. However, a trial to compare outcomes for those who undergo LT for perihilar cholangiocarcinoma with or without neoadjuvant therapy, would be extremely difficult to conduct given the rarity of this disease and ethical considerations associated with unacceptably high recurrence and mortality rates historically reported with LT alone, even for incidentally discovered, and therefore presumably very early, perihilar cholangiocarcinoma. Another limitation was that a large proportion of patients were from one center, creating a potential for bias. To address this concern, outcomes were compared between this center and all others, and there were not statistical differences (figures 3c and 3d), even after correcting for variability in selection, staging and brachytherapy. The fact that we did not find a difference underlines the broader applicability of the protocol. Finally, due to heterogeneity in duration, type and dose of maintenance chemotherapy administered at different centers, we were unable to determine the independent impact of maintenance chemotherapy."

The authors concluded that their "study confirms excellent outcomes of neoadjuvant chemoradiotherapy followed by LT for patients with perihilar cholangiocarcinoma across 12 U.S. institutions with variable neoadjuvant protocols. The assigned MELD score adjustment set by current UNOS/OPTN policy appears to be appropriate based on an observed dropout rate of 11.5% per 3-month increment. Patient selection clearly impacts outcomes as a 3-fold increased risk of recurrence and death post-transplant was seen in patients with larger tumors, metastatic disease at transplantation, direct tumor biopsy and prior history of malignancy. While we could not find an independent benefit from the addition of brachytherapy, it is clear that at a minimum, EBRT with concomitant chemotherapy should be provided. The central challenge for the future will be to gain a greater understanding of the tumor biology in order to reduce waitlist dropout and post-transplant recurrence either by further refinements in patient selection or, ideally, by more effective chemoradiotherapy."

Murad SD, Kim WR, Therneau T, et al. Predictors of pre-transplant dropout and post-transplant recurrence in patients with perihilar cholangiocarcinoma. Hepatology 2012 doi: 10.1002/hep.25629.

This is the e-publication of an accepted manuscript.

Murad and colleagues performed a retrospective analysis of data collected from patients who received a liver transplantation after neoadjuvant chemoradiotherapy and a staging laparotomy/laparoscopy at the Mayo Clinic from January, 1993 to October, 2010. The goals of the analysis were to "identify independent predictors of dropout before transplantation, as well as predictors of cancer recurrence after transplantation."

The definition of "dropout" was "positive staging, tumor metastasis, death or withdrawal due to intolerable side effects before transplantation." Recurrence was defined as "radiographic or pathologically confirmed evidence of cholangiocarcinoma post-transplantation." Survival was calculated using the Kaplan Meier method and compared using the log-rank test. There was no control group.

A total of 199 patients were enrolled; the median age was 51 years (range, 19 – 70). Sixty-two (31%) of these patients dropped out prior to transplantation; the median time of dropout was 4.7 months (range, 1.1 – 17.1). The multivariable analysis identified four independent predictors of dropout: mass size three cm or greater; positive or suspicious intraluminal brushing or biopsy; elevated CA 19-9; and higher MELD score.

Liver transplantation was performed in 137 patients; the median age for this group was 50.6 years (range, 19 – 67). However, the surgery was performed at the Mayo Clinic for only 131 of these patients; the median age and range were not reported for just these patients. Survival rate at 1, 2, and 5-years after transplantation for the 131 patients was 91% (95% CI, 86 – 96), 85% (95% CI, 79 – 91) and 71% (95% CI, 62 – 80), respectively. Recurrence-free survival at 1, 2 and 5 years for the 131 patients was 87% (95% CI, 82 – 93), 80% (95% CI, 72 – 87) and 68% (95% CI, 59 – 77), respectively. During multivariable analysis, an elevated CA 19-9 at presentation, the presence of complete portal vein encasement and the presence of residual tumor tissue on explants were the only independent predictors of recurrence after transplantation.

The authors noted that "[O]ur results continue to demonstrate excellent outcomes following neoadjuvant therapy and liver transplantation for early-stage perihilar CCA, similar to earlier studies. Indeed, our 71% 5-year post-transplant survival is similar to the 68% for all deceased liver transplants based on the latest Organ Procurement and Transplantation Network data. We believe this is achieved by a combination of rigorous selection criteria and the effectiveness of neoadjuvant radiation and chemotherapy to eliminate or at least contain the tumor while awaiting transplantation."

Murad and colleagues also noted three limitations to their analysis. They first note that "although this is the largest series to date, overall numbers from a statistical standpoint are still small, especially for the analysis of recurrence risk. We therefore limited the list of potential predictors to only the most clinically relevant. Second, even though most patients are followed at our institution, we could not assess final outcome for ten patients who left our clinic after dropout, who typically returned to their local centers for palliative care. Lastly, despite all our efforts to obtain a definite diagnosis in patients whose clinical picture is highly compatible with CCA, we were unable to obtain definite evidence in 16 patients. However, we showed that excluding these patients did not significantly alter our results."

The authors concluded that "patients who undergo neoadjuvant chemoradiation followed by liver transplantation have excellent 5-year recurrence-free survival."

Neuroendocrine Tumors

Two review articles were identified. One article (Le Treut, 2008) presented an analysis of data from transplant centers in France. The second article (Mathe, 2011) presented the results of a systematic review of the literature.

Le Treut YP, et al. Predictors of long-term survival after liver transplantation for metastatic endocrine tumors: an 85-case French multicentric report. American Journal of Transplantation 2008;8:1205-1213.

Le Treut and colleagues conducted a retrospective, multi-center (17 centers) analysis of 85 patients with liver metastases due to NET who received a liver transplantation in France between 1989 and 2005. The goal of the analysis was to find prognostic factors for long term survival. Quality of life outcomes were not reported. There was no control group. The authors stated that "[C]omparisons were made using the Student, Mann-Whitney or chi-square test. The main evaluation criterion was overall 5-year survival." A prognostic score was developed during the analysis (called a patient selection tool by the authors) using primary tumor location and presence/absence of hepatomegaly. With regards to the primary tumor location, zero points were assigned to the DT (primary tumor in the bronchial tree or digestive tract) and UD (primary tumor in an undetermined site) groups and one point to the DP group (primary tumor in the duodenum or pancreas). For hepatomegaly, zero points were assigned for the absence of hepatomegaly and one point for the presence of hepatomegaly. Patients were then classified into three groups: zero points; one point; and two points. The authors noted the "risk model was created using a two-point scale (0 or 1) for each variable identified by multivariate analysis. The power of the model in predicting long-term survival was determined by analyzing risk groups with Kaplan-Meier curves and the log-rank test."

The authors stated that "the indication for LTx was decided at each center. However, for the purpose of this study, we classified indications into three general categories, i.e. 'hormonal syndrome' in patients presenting life-threatening or debilitating hormone-related symptoms, 'tumor bulk' in patients presenting pain or debility associated with enlargement of the liver and 'oncological' in patients with low-grade symptoms." The primary tumor was located in the duodenum or pancreas in 40 patients (DP group); in the bronchial tree or digestive tract in 31 patients (DT group); and in an undetermined site in 14 patients (UD group).

The mean ± SD age was 45 ± 11 years (range, 18 - 64). Eighty-seven percent of the tumors were well-differentiated and the remaining 13% were poorly differentiated. Eighty percent of patients had surgical treatment prior to transplantation (ablation, resection or exploratory laparotomy). Ninety-four percent of patients in the DT group and 65% of patients in the DP group had a resection of the primary tumor. Eighty-two percent of patients had chemotherapy prior to transplantation. The indication for transplantation was "oncological" in 42% of cases; "tumor bulk" in 27%; "hormonal syndrome" in 24%; according to the authors, the remaining cases (7%) "involved presumed HCC including one case of fibrolamellar variant and one case associated with post hepatitis B cirrhosis. These cases correspond to the three patients in whom small bowel primary tumors were discovered during or after LTx. The remaining three patients presented severe complications of TACE, i.e. ischemic cholangitis in two cases and subacute liver failure in one case."

The authors stated that "[T]welve patients (14%) died during the postoperative period (interval, 2 to 157 days) due mainly to surgical complications such as hemorrhage, pancreatitis and sepsis. Three-month mortality was also 14%." The authors noted that "[N]o patient was lost from follow-up. Mean duration of follow-up was 46 ± 47 months (range, 0 - 202). In 68 cases (80%) LTx had been performed 5 or more years before the end of follow-up. The cause of death after discharge was tumor recurrence in all but five patients who died due to delayed surgical complications with no sign of recurrence. Overall actuarial survival was 72%, 67%, 59%, 51% and 47% at 1 to 5 years respectively (with 24 patients still at risk). Median survival was 56 months (range, 0 - 202). Disease-free survival was 56%, 45%, 37%, 22% and 20% at 1 to 5 years, respectively (Figure 2). Survival after diagnosis of liver metastases was 92%, 88%, 78%, 73% and 69% at 1 to 5 years, respectively."

Results of multivariate analysis identified three independent risk factors for poor prognosis: upper abdominal exenteration, duodenal or pancreatic primary tumor and hepatomegaly (defined by the authors as liver enlargement of 20% or more beyond standard liver volume). Patient age was not found to be a risk factor for poor prognosis. For the analysis of the patient selection tool, a significant difference in survival was not found between patients with a classification of zero or one; or for patients with a classification of one or two. A significant difference in survival was found between patients with a classification of zero or one versus those patients with a classification of two ($p < 10^{-7}$).

Based on the results of their analysis and their review of the literature, the authors concluded that liver transplantation for patients with liver metastases due to NET is useful for operable patients regardless of age provided that cardiac function is acceptable, especially for patients with a carcinoid tumor; for patients with unresectable liver metastases causing incapacitating hormone- or tumor-related symptoms or even low-grade symptoms; for patients with a well-differentiated tumor type and a Ki67 index of less than 10%; for patients without documented extrahepatic disease; and for patients who have undergone resection of the primary tumor. The authors stated that their patient selection tool was useful while acknowledging that it was developed using a retrospective analysis and therefore the selection tool will require further confirmation in a larger relevant patient population.

Mathe Z, et al. Liver transplantation for hepatic metastases of neuroendocrine pancreatic tumors: a survival-based analysis. Transplantation 2011;91:575-582.

Mathe and colleagues conducted a systematic review of the literature. The goals of the analysis were to perform a survival analysis and identify potential prognostic factors of survival. Quality of life outcomes were not reported. There was no control group. Twenty studies were included in the analysis; the total sample size was 89 patients with hepatic metastases due to a pancreatic NET who received a liver transplantation. Sixty-nine patients had an endocrine pancreatic tumor; nine patients had a carcinoid tumor; and 11 patients were classified only as pancreatic NET primary. The reason for liver transplantation (e.g., symptom control) was not reported.

The median patient age was 46 years (range, 11 - 64); two patients were ≤ 18 years old (ages 11 and 13). The median follow-up was 16 months (range, 0.2 - 123). The recurrence-free survival rate at 1 year, 3 years and 5 years was 84%, 47% and 47%, respectively. However, data on tumor recurrence were not available for 30 patients.

The calculated median survival was 41 months (95% confidence interval, 22 - 76); the calculated mean ± SD survival was 54.45 ± 6.31 months. The cumulative 1-year, 3-year and 5-year patient survival rate was 71%, 55% and 44%, respectively. No difference in the survival rate was seen between patients with a carcinoid tumor and those with an endocrine pancreatic tumor. The calculated 1-year, 3-year and 5-year patient survival rate was 79%, 67% and 54%, respectively, for patients who received only a liver transplant versus a cumulative 1-year, 3-year and 5-year patient survival rate of 64%, 40% and 33%, respectively, for patients who received a simultaneous resection of the primary tumor (comprised of upper abdominal exenteration for 23 patients) and liver transplantation; this difference was statistically significant (p = 0.01).

Upon multivariate analysis, patient age of 55 years or older and simultaneous removal of the primary tumor and liver transplantation were found to be significant independent predictors of survival (p = 0.02 and p = 0.01, respectively). A scoring system was developed using these two independent predictors where age less than 55 years was assigned zero points; age 55 years and older was assigned one point; liver transplantation only was assigned zero points; and liver transplantation plus removal of the primary tumor was assigned one point. The calculated 1-year, 3-year and 5-year patient survival rate was 89%, 77% and 61%, respectively, for a total score of zero; 61%, 40% and 40%, respectively, for a total score of one; and 57%, 29% and 0%, respectively, for a total score of two.

The authors concluded that their study results confirmed that patients should be 55 years old or younger and that the primary tumor should be resected prior to transplantation. In addition, they stated that good results can be achieved with liver transplantation for patients with liver metastases due to pancreatic NET when using these two patient selection criteria.

<u>Hemangioendothelioma</u>

Three articles were identified for further review during the literature search. One article (Mehrabi, 2006) presented the results of a systematic review of the literature. The second article (Lerut, 2007) presented an analysis of data from the European Liver Transplant Registry. The third article (Rodriguez, 2008) presented an analysis of OPTN data.

Mehrabi A, et al. Primary malignant hepatic epithelioid hemangioendothelioma: a comprehensive review of the literature with emphasis on the surgical therapy. Cancer 2006; 107:2108-2121.

To examine the various types of treatment for primary HAE including liver resection, liver transplantation, chemotherapy, radiotherapy and immunotherapy, Mehrabi and colleagues performed a review of the literature from 1984 to 2005 "because of the rarity of this tumor and its unpredictable natural history, it is impossible to assess the effectiveness of these respective therapies."

The data from 402 patients were analyzed but information regarding age was available for only 327 patients; the mean age was 41.7 years (range, 3-86). The number or percentage of patients who were ≥ 65 years old was not reported. The authors noted that an "analysis of all reported patients indicated that the clinical manifestation of HEH was heterogeneous and varied from asymptomatic patients to patients with portal hypertension or hepatic failure." Information regarding the location of HAE at the time of diagnosis was available for 306 patients. The authors reported that 87% of patients presented with a multifocal tumor that involved both liver lobes while only 13% of patients had a unifocal tumor.

Two hundred eighty-six patients had adequate documentation of the treatment methods used; 128 of these patients (44.8%) underwent liver transplantation (LTx); 71 of the 286 patients (24.8%) received no treatment; 60 of the 286 patients (21%) received chemotherapy or radiotherapy; and 27 of the 286 patients (9.4) underwent liver resection (LRx). The indication for liver transplantation was not reported. The author did state that "in the majority of patients, an oncologic resection is impossible because of the multicentricity of the lesions or anatomic difficulties."

Regarding outcomes, the authors noted that "the survival data were available for 253 patients (Table 7). Among 101 patients who underwent LTx and had follow-up data available, 77% were alive at a mean follow-up of 45 months (median and/or range not reported), whereas 23% of patients who had a mean follow-up of 41 months (median and/or range not reported) had died at the time they were reported. After LRx, the survival rate was 95% for all patients, with a mean observation time of 38 months in the patients who remained and with a mean survival of 15 months in the patients who died. The overall percentage of patients who remained alive, whether they received any kind of treatment or no treatment, was 83.4%, 55.8%, and 41.1% after 1 year, 3 years, and 5 years, respectively (Fig 3). The surgical therapies, LTx and LRx, had the best survival rates with 5-year survival rates of 54.5% and 75%, respectively. The survival rates decreased markedly to 30% and 4.5% for patients who received chemotherapy/radiotherapy and patients who went without treatment, respectively (Fig 3). Although the results of LRx have been good, it should be noted that HEH in most patients is not resectable because of its nature, which tends to involve the liver in a diffuse manner. Among the patients who received chemotherapy or radiotherapy, 58% remained alive at a mean follow-up of 43 months, and 42% died with a mean follow-up of 26 months. Forty percent of the patients who did not receive any kind of treatment remained alive after a mean follow-up of 32 months; however, 60% of patients died after mean of 8 months."

The authors suggested that for "patients who have massive involvement of the liver, a total hepatectomy with LTx is the best therapeutic choice." The authors concluded that "the decision on a treatment strategy for HEH has to be tailored to each patient, and the individual rate of progression, severity of signs and symptoms, and response to other treatment modalities may be important determinants for decision making. Because of the lack of randomized clinical trials, the definite role of the treatment modalities described above cannot be determined to date."

Lerut JP, et al. The place of liver transplantation in the treatment of hepatic epithelioid hemangioendothelioma. Annals of Surgery 2007;246:949-957.

Lerut and colleagues conducted a retrospective analysis on 59 patients with the diagnosis of HAE in the European Liver Transplant Registry who received a transplant between 1989 and 2004. The authors sent a questionnaire to 32 European transplant centers to inquire about pre-transplant, peri-transplant and post-transplant outcomes; a total of 216 items were included in the questionnaire including quality of life outcomes using the Karnofsky score. There was no control group. The goal of the analysis was to determine a "better definition of the value of liver transplantation (LT) in the current management of" HAE.

Ten percent of the questionnaires lacked a response for 21 to 30 items; 18.6% of the questionnaires lacked a response for more than 30 items. The median age at the time of transplant was 42 years (range, 4 - 65); two patients were less than 15 years old but the number or percentage of patients who were 65 years old was not reported. Pre-transplant treatment, including various combinations of liver resection, chemotherapy and radiotherapy, was administered to 30.5% of patients. Median follow-up time was 78.5 months (range, 1 - 245) after transplant.

Tumor was found in both lobes of the liver in 86% of patients; the percentage of patients with extrahepatic disease was not reported. Nineteen percent of patients were asymptomatic.

The perioperative (defined as less than 3 months since transplantation) mortality rate was 1.7%; mortality three months or more after transplantation was 22%. Patient survival rates at 1, 5 and 10 years were 93%, 83% and 72%, respectively. Disease recurrence was seen in 23.7%; the median time to recurrence was 49 months (range, 6 - 98); nine patients died due to tumor recurrence. The disease-free survival rate at 1, 5 and 10 years was 90%, 82% and 64%, respectively. Regarding the quality of life outcome, the "[M]edian Karnofsky score improved in 46 long-term survivors from 90 (range, 20 - 100) pre-LT to 100 post-LT (range, 80 - 100)."

The authors stated that the higher 5- and 10-year survival rates found in their study, compared to previously reported survival rates, "validates" the role of liver transplantation in the treatment regimen of HAE. Their study also "confirms" that the presence of extrahepatic disease is not a formal contraindication to liver transplantation. In conclusion, the authors noted that the prognosis might be improved by combining "radical surgery" and neoadjuvant nonsurgical therapies.

Rodriguez JA, et al. Long-term outcomes following liver transplantation for hepatic hemangioendothelioma: The UNOS experience from 1987 to 2005. Journal of Gastrointestinal Surgery 2008;12:110-116.

Rodriguez and colleagues presented the results of a retrospective analysis of the OPTN transplantation database. The data were from 110 patients with HAE who received a liver transplant between 1987 and 2005. The authors noted that the "best treatment strategy for patients with borderline resectable HEH has not been determined. To assess the utility of OLT in patients with extensive intrahepatic disease, this study evaluated patient and graft survivals after transplantation in a large, multi-institutional cohort of patients with HEH." Quality of life outcomes were not reported. There was no control group.

The median age was 36 years (range, 0 - 70); 71% were older than 18 years of age but the number or percentage of patients who were ≥ 65 years old was not reported. The median duration of follow-up after transplantation was 24 months (range, 0 - 181).

Except where indicated the results were presented for all 110 patients (i.e., the results for only the adults were not reported separately). There was one operative death and two deaths within 30 days of transplant; the 30-day mortality rate was 2.4%. The patient survival rate for adults at 1-, 3- and 5-years was 81%, 72% and 67%, respectively. Thirty-two percent of the 38 patients who died during long-term follow-up died of recurrent HAE (mainly involving distant sites according to the authors).

Median liver graft survival at 1-, 3- and 5-years was 70%, 60% and 55%, respectively. Twelve patients (11%) required a second transplantation; four of these patients required a third transplantation. Reasons for retransplantation included graft nonfunction, vascular thrombosis and biliary complications.

Results of an analysis to determine the impact of various study variables on patient survival revealed that patients who are sicker (i.e., require hospitalization prior to transplant) had a lower 5-year survival (44%) compared to nonhospitalized patients (72%; $p = 0.01$). The 5-year survival rate for patients who required care in the intensive care unit was 39% versus 65% for those who did not ($p = 0.02$). Age did not influence patient survival.

The authors concluded that liver transplantation for patients with HAE is "associated with favorable outcomes." In addition, given this and the "propensity for recurrence after liver resection, liver transplantation should be considered as a first-line treatment in patients who would otherwise require major hepatic resection, including selected patients with extrahepatic disease."

4. MEDCAC

A MEDCAC meeting was not held.

5. Evidence-based guidelines

Cholangiocarcinoma

NCCN

The National Comprehensive Cancer Network (NCCN) has an evidence-based clinical practice guideline for Hepatobiliary Cancers (Version 2, 2012) that addresses intrahepatic CCA and extrahepatic CCA. The guideline did not mention the use of liver transplantation for intrahepatic CCA.

For extrahepatic CCA, the guideline noted that "[H]ighly selected" patients with unresectable disease "may be transplant candidates." The guideline stated that "transplantation is the only other potentially curative option for patients with extrahepatic cholangiocarcinoma. This option is only recommended for highly selected patients with either unresectable disease with otherwise normal biliary and hepatic function or underlying chronic liver disease precluding surgery. There is retrospective evidence showing selected patients with hilar cholangiocarcinoma receiving preoperative chemoradiation therapy followed by liver transplantation to have significantly improved overall survival compared with patients undergoing resection. Nevertheless, there were substantial differences in the characteristics of patients in the two treatment groups in this study. The panel encourages continuation of clinical research in this area." NCCN assigned a category of evidence and consensus grade of "2A" to this recommendation, which indicates that the recommendation is "[B]ased upon lower-level evidence, there is uniform consensus that the intervention is appropriate."

American Association for the Study of Liver Diseases (AASLD)

On its website AASLD stated that it "is the leading organization of scientists and healthcare professionals committed to preventing and curing liver disease." In a practice guideline published in 2010 titled "Diagnosis and Management of Primary Sclerosing Cholangitis," AASLD noted the use of the Mayo Protocol for patients with hilar, unresectable CCA but also noted that the protocol "has yet to be applied outside of a single center, and, therefore, whether this protocol can be generalized is unclear." The guideline recommended that patients with early stage, unresectable CCA be considered for liver transplantation following neoadjuvant therapy by experienced transplant centers. AASLD assigned a grade of "IB" to this recommendation, where a "I" stands for a "strong" strength of recommendation and a "B" means that the recommendation was based on a "moderate (further research may change confidence in the estimate of the clinical effect)" quality of evidence (Chapman, 2010).

Neuroendocrine Tumors

NCCN has an evidence-based clinical practice guideline titled Neuroendocrine Tumors (Version 1, 2011). The guideline does not mention the use of liver transplantation for NETs.

In 2005 AASLD published a practice guideline titled the "Evaluation of the Patient for Liver Transplantation." The guideline notes that the outcome of liver transplantation in patients with metastatic neuroendocrine tumors has been mixed and recommends that liver transplantation in these patients "should be confined to highly selected patients who are not candidates for surgical resection in whom symptoms have persisted despite optimal medical therapy." AASLD assigned a quality of evidence grade of "III" to this recommendation, which means that the recommendation was based on the opinions of respected authorities and descriptive epidemiology (Murray and Carithers, 2005).

Hemangioendothelioma

In its 2005 practice guideline titled the "Evaluation of the Patient for Liver Transplantation," AASLD noted that patients with HAE have a better prognosis than do patients with HCC and do not have evidence of significant underlying liver disease. Consequently, "transplantation is uncommonly required." However, the guidelines stated that transplantation is not necessarily contraindicated for patients with large tumors. AASLD recommended that liver transplantation should be considered for patients with unresectable HAE. A quality of evidence grade of "III" was assigned to this recommendation, which means that the recommendation was based on the opinions of respected authorities and descriptive epidemiology (Murray and Carithers, 2005).

6. Professional Society Position Statements

There were no professional society position papers found.

7. Expert Opinion

Except as may be noted elsewhere in this memorandum, we have not received expert opinion on this issue.

8. Public Comments

CMS received six timely public comments during the initial public comment period.

The comments can be viewed in their entirety on our website at: https://www.cms.gov/medicare-coverage-database/details/nca-view-public-comments.aspx?NCAId=259&ExpandComments=n&ver=1&NcaName=Liver+Transplantation+for+Malignancies+(1st+Recon)&bc=ACAAAAAAIAAA&

Public Comment Period **03/29/2012 – 04/28/2012**

During the 30-day comment period on the proposed decision CMS received five comments. All commenters supported some type of coverage.

References to Published Materials

Commenters referenced three articles for review by CMS: Murad, Kim, Harnois (2012); Murad, Kim, Therneau (2012); and Roberts (2004). They submitted the article Murad, Kim, Harnois (2012) in support of their contention that the success at Mayo and Nebraska in transplantation for cholangiocarcinoma can be replicated elsewhere. The commenter contends that Murad, Kim, Therneau (2012) suggests based on retrospective data modeling that there is no increase in drop-out rate or recurrence based on age and advocates for this treatment for Medicare aged beneficiaries with cholangiocarcinoma. Roberts (2004) provides data on general liver transplantation results which they use as a comparison to transplantation in cholangiocarcinoma.

CMS Response: We reviewed the three articles and both Murad (2012) articles are added to the evidence section. The multicenter study Murad, Kim, Harnois (2012) suggests the potential for increased geographic options that patients may have for treatment. The Murad, Kim, Therneau (2012) strives to draw conclusions related to age based on retrospective data modeling, but it does not identify the number of individual Medicare aged patients, which is a significant limitation.

We also note the time period for Murad, Kim, Harnois (2012) and Murad, Kim, Therneau (2012) overlap substantially with the time period for the Heimbach (2006) and the Becker (2008) analyses and it appears there is overlapping analysis, i.e., many of the same patients are those reported in the Murad (2012) studies. This would double count the same patient results and create a misperception that the evidence base is greater than it really is. As it is difficult to determine which patient results are already reported in previous studies, the two Murad (2012) articles add little to the evidence base. Roberts (2004) is not persuasive in our review of cholangiocarcinoma as we do not believe transplantation for other indications can be extrapolated to cholangiocarcinoma.

Local Contractor Discretion

All commenters express appreciation for the CMS expansion of coverage in our proposed decision, but three of them recommend that coverage for cholangiocarcinoma instead be standardized such as by use of existing protocols approved by the Organ Procurement and Transplant Network while at the same time acknowledge the need to carefully select patients. Commenters express concerns with potential delays and ensuing appeals with coverage residing at local contractor discretion. While they contend that the lack of evidence in the Medicare population is because of Medicare noncoverage, commenters agree with the clinical focus expressed by CMS in its analysis that highly emphasizes the need to carefully select patients.

CMS Response: We appreciate the support for coverage expansion. However, we do not believe that the available evidence with its limitations can support a broad positive national coverage decision at this time. We believe that coverage of liver transplantation in patients with these three rare malignancies, where the evidence base is understandably sparse for all ages, should be determined by our local administrative contractors, who are in a better position to consider characteristics of individual beneficiaries and the performance of transplant centers within their jurisdictions.

Quality of Life and Patient Indication

A commenter said there is an unpublished article submitted for peer review related to quality of life outcomes. The same commenter defined unresectable as, "if they have disease occurring in the setting of advanced underlying liver disease, or if bilobar involvement of malignancy to the second order biliary radicals. As stated in our previous publications, we always include consultation with an experienced hepatobiliary surgeon to be sure our interpretation of unresectable is accurate."

CMS Response: *While we appreciate the comments, an unpublished article does not carry substantive evidentiary weight. We note that the article on quality of life outcomes is not available for public review. The definition of unresectable that is provided by the commenter is subjective and may differ based on the individual doing the patient assessment.*

VII. CMS Analysis

A. Introduction

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally by Medicare (§1862(l) of the Act).

In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, section 1862(a)(1) of the Social Security Act in part states, with limited exceptions, no payment may be made under part A or part B for any expenses incurred for items or services:

- Which, are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member (§1862(a)(1)(A)), or
- In the case of research conducted pursuant to section 1142, which is not reasonable and necessary to carry out the purposes of that section. ((§1862(a)(1)(E)).

CMS asked the following questions during our review:

1. Is the evidence adequate to conclude that liver transplantation improves health outcomes of Medicare beneficiaries with cholangiocarcinoma?
2. Is the evidence adequate to conclude that liver transplantation improves health outcomes of Medicare beneficiaries with liver metastases due to a neuroendocrine tumor?
3. Is the evidence adequate to conclude that liver transplantation improves health outcomes of Medicare beneficiaries with hemangioendothelioma?

Cholangiocarcinoma

CCA is an uncommon but aggressive disease (Becker, 2008). The majority of patients survive less than one year when treated with nonsurgical therapies (Becker, 2008). According to Grossman and Millis (2010), "[S]urgical resection is the mainstay of treatment for periductal CCA and yields 5-year survival rates of 27% to 44%. However, tumor invasion into the main portal vein, common hepatic artery, or one lobe of the liver with invasion of the contralateral branch of the portal or hepatic artery renders the tumor unresectable. Additionally, CCA arising in the setting of primary sclerosing cholangitis (PSC; Fig. 1) is associated with a likelihood of multifocal disease and a high risk of recurrence following resection; thus, such patients are prohibited from undergoing resection."

Liver transplantation is another surgical option for patients with CCA. According to the 2012 NCCN clinical practice guideline, liver transplantation "is the only other potentially curative option for patients with extrahepatic cholangiocarcinoma." In their review, Grossman and Millis (2010) noted that "[I]n 2000, the Cincinnati registry examined the results of 207 patients who underwent liver transplantation for CCA. The overall 1-, 2-, and 5-year survival rates were 72%, 48%, and 23%, respectively. Among those patients who suffered recurrence, the recurrence was detected within 2 years for 84%; recurrence occurred in the liver allograft for 47% and in the lungs for 30%."

In our review of the evidence published over the past 10 years which consisted of retrospective studies, we found 1-year and 5-year survival rates of 91% at 1-year and 76% at 5-years as quoted by Heimbach and colleagues (2006); the 1-year survival rate was 74% and the 5-year rate was 38% in the Becker analysis from 2008. While the lack of more robust study designs such as randomized, controlled studies introduces the possibility of bias and confounding, it would be challenging to operationalize this type of study with this relatively rare malignancy.

Neither analysis contained a large number of Medicare-aged patients. In Heimbach (2006) the age range was 22 - 66 years and only eight patients were older than 60 years. In the Becker (2008) analysis the age range was 18 - 73 years but it is unclear how many of these patients were 65 years old or older. In addition, in neither article were the results reported specifically in those patients 65 years old or older. While Becker and colleagues (2008) did not observe an age-related impact on patient survival, Heimbach and colleagues (2006) did find an increased risk for recurrence after transplantation in patients older than 45 years, which led the authors to conclude that older patients "are at a higher risk of disease recurrence." The effect of comorbidities on survivorship is also not known. It is unclear how the reported results can be generalized to individual patients in the Medicare population.

Another limitation is the definition of unresectable disease. It is unclear in the Heimbach (2006) article and not addressed at all in the Becker (2008) analysis. This is important because according to the NCCN (2012) clinical practice guideline, liver transplantation is "only recommended for highly selected patients with either unresectable disease with otherwise normal biliary and hepatic function or underlying chronic liver disease precluding surgery." This leads to doubt regarding the characteristics of the patients in the Heimbach (2006) and the Becker (2008) analyses, which then leads to uncertainty about the reported patient survival rates.

It is unclear if more than two transplant centers (Mayo Clinic/Rochester; University of Nebraska) have used the treatment protocol used in Heimbach (2006). This introduces uncertainty as to whether similar results reported in Heimbach (2006) can be achieved in other transplant centers.

No quality of life outcomes were reported in the evidence we reviewed. CCA is an aggressive disease that can lead to significant morbidity. Some patients will be significantly clinically compromised due to the adverse impact of the disease itself as well as any side effects from therapies and procedures. Liver transplantation is an intensive surgical procedure with inherent risks. All of these factors are taken into consideration by a patient and the patient's physicians when deciding whether or not to proceed with transplantation. Quality of life outcomes are important pieces of information to have during this decision-making process.

Two literature articles not identified during our initial literature search but presented in the second public comment period (Murad, Kim, Harnois, 2012;Murad, Kim, Therneau, 2012) contained clinical evidence from patients who received a liver transplant in the U.S. and were added to the Internal Technology Assessment section of this memorandum. The time period for each of these articles overlaps substantially with the time period for the Heimbach (2006) and the Becker (2008) analyses. This strongly suggests that the majority of the evidence in the two Murad articles is based on the same subjects as in the Heimbach (2006) and Becker (2008) articles. This would result in a double counting and make the evidence base appear larger. The analyses in the Murad articles suffer from the same limitations (e.g., a lack of Medicare-aged patients; retrospective analysis study design) and do not offer any new evidence except to note that since 1993 12 centers in the U.S. have performed liver transplantation in at least three patients using the neoadjuvant protocol. The 5-year recurrence-free survival rate reported in the two Murad articles is slightly lower (65% - 71%) than that reported in the Heimbach (2006) analysis (76%).

It is important to note that OPTN has an allocation policy regarding liver transplantation for patients with extrahepatic CCA. As mentioned earlier, NCCN supports the use of liver transplantation for highly selected patients with unresectable disease or underlying chronic liver disease precluding surgery. It is noteworthy that NCCN also encourages the conduction of more clinical research, particularly regarding the use of other anti-cancer therapies prior to liver transplantation to lessen the tumor burden and/or reduce the risk of recurrence.

Upon review of the available evidence which has accumulated since the 2002 NCD, we believe that the evidence base does not support a broad national coverage decision, mainly due to the significant imprecision about estimates of benefit and harm. It is not apparent at this time that the available evidence clearly and broadly distinguishes patients who will experience an improved outcome from those who will derive harm such as postoperative complications or adverse effects from the life-long immunosuppressive medication that is necessary after transplantation. There are inherent challenges in developing durable conclusions about a complex surgical procedure such as liver transplantation for such rare malignancies when there are no randomized clinical trials. It is also daunting to create a general profile of a clinically appropriate patient in the use of liver transplantation in CCA. Though technical factors and underlying patient physiology would be expected to vary little among geographic regions, the practice of medicine with regards to organ transplantation reflects the need to reasonably account for distinctions based on patent selection, transplant centers and their surgical staff. Moreover, we recognize the need for timely judgment and decisions for transplantation for these lethal and complex rare end stage liver diseases. In this aggressively lethal disease, this treatment may offer the only relief. It is unclear which patients could benefit in this rare disease, but some patients do appear to benefit. Therefore, Medicare coverage of this treatment may be best considered only in carefully selected patients on a case by case basis at this time.

Neuroendocrine Tumors (NET)

A NET is a rare cancer (Blonski, 2005) with a highly variable clinical course and prognosis (Chan, 2011). Some patients are asymptomatic while other patients have symptoms related to the excessive secretion of hormones by the tumor (Chan, 2011). According to Harring (2011), a NET that metastasizes to the liver is associated with significant morbidity and mortality and consequently has a particularly poor prognosis compared to patients with a NET without liver metastasis. The 5-year survival rate for patients with liver metastases who receive only supportive care is reported to be 0 - 20% (Harring, 2011). The 5-year survival rate after resection of the liver metastases, which is the primary treatment, is reported to be 60 - 80% (Grossman and Millis, 2010). However, if at least 80 - 90% of the liver metastases are determined to be unresectable and/or if symptoms cannot be adequately controlled using medical therapy, then liver transplantation is an option (Grossman and Millis, 2010).

In our review of the evidence published over the past 10 years, we found a 1-year survival rate of 71 - 72% and a 5-year survival rate of 44 - 47%. The recurrence-free survival rate was more variable between the two analyses that we reviewed; Le Treut (2008) reported a 1-year recurrence-free survival rate of 56% while Mathe (2011) reported a rate of 84%. For 5-year recurrence-free survival, Le Treut (2008) reported a rate of 20% while Mathe (2011) reported a rate of 47%. This discrepancy may be in part due to the shorter follow-up time in the Mathe analysis. It may also be due to the small number of cases that were eligible for the recurrence analysis. There was also a difference in patient population between the two analyses. In the Mathe (2011) analysis a large majority of patients had a NET of pancreatic origin while for the Le Treut (2008) analysis the origin of the NET was widely variable. All of these factors may also have impacted the 5-year survival rate reported by Mathe and colleagues (2011), leading to uncertainty in the prognosis.

The study outcomes are from retrospective analyses. While the lack of more robust study designs such as randomized, controlled studies introduces the possibility of bias and confounding, it would be challenging to operationalize this type of study with this relatively rare malignancy. Neither analysis contained a large number of Medicare-aged patients. In the articles reviewed no patients were 65 years old or older. Of note, there is a discrepancy between the age-related results of the analysis to identify prognostic factors of survival. Le Treut (2008) found that patient age was not a risk factor for prognosis (provided that cardiac function is acceptable) while Mathe (2011) found that a patient age of 55 years or older was a statistically significant independent predictor of survival. This finding led Mathe (2011) to conclude that liver transplantation should be performed in patients who are 55 years old or younger. The effect of comorbidities on survivorship is also not known. It is unclear how the reported results can be generalized to individual patients in the Medicare population.

No quality of life outcomes were reported in the evidence we reviewed. Given that some patients undergo liver transplantation for symptom control it is surprising that quality of life outcomes have not been assessed. Patients with liver metastases due to a NET can have aggressive disease that can lead to significant morbidity and mortality. Some patients will be significantly clinically compromised due to the adverse impact of the disease itself as well as side effects from any therapies and procedures, especially an intensive procedure such as transplantation. All of these factors may be taken into consideration by a patient and the patient's physicians when deciding upon a treatment plan. Quality of life outcomes are important for the decision-making process.

During our review we found only one guideline that addressed the use of liver transplantation for patients with liver metastases due to a NET. The 2005 AASLD guideline noted that "the outcome of liver transplantation in patients with metastatic neuroendocrine tumors has been mixed." Of note, this recommendation was based upon opinion and descriptive epidemiology rather than evidence from clinical studies. It is also noteworthy to CMS that while NCCN has a clinical practice guideline specifically for NET, it does not mention liver transplantation. Finally, we note that OPTN has not implemented a MELD exception for liver allocation for neuroendocrine tumor liver metastases.

Upon review of the available evidence which has accumulated since the 2002 NCD, we believe that the evidence base does not support a broad national coverage decision, mainly due to the significant imprecision about estimates of benefit and harm. It is not apparent at this time that the available evidence clearly and broadly distinguishes patients who will experience an improved outcome from those who will derive harm such as postoperative complications or adverse effects from the life-long immunosuppressive medication that is necessary after transplantation. There are inherent challenges in developing durable conclusions about a complex surgical procedure such as liver transplantation for such rare malignancies when there are no randomized clinical trials.

It is also daunting to create a general profile of a clinically appropriate patient in the use of liver transplantation in NETs. Though technical factors and underlying patient physiology would be expected to vary little among geographic regions, the practice of medicine with regards to organ transplantation reflects the need to reasonably account for distinctions based on patent selection, transplant centers and their surgical staff. Moreover, we recognize the need for timely judgment and decisions for transplantation for these lethal and complex rare end stage liver diseases. In this aggressively lethal disease, this treatment may offer the only relief. It is unclear which patients could benefit in this rare disease, but some patients do appear to benefit. Therefore, Medicare coverage of this treatment may be best considered only in carefully selected patients on a case by case basis at this time.

Hemangioendothelioma

Primary malignant HAE is a rare cancer (Hertl and Cosimi, 2005). The clinical course is highly variable; some patients present with hepatic failure while other patients are asymptomatic (Mehrabi, 2006). In 2007 Lerut stated that the course of treatment for HAE is "far from standardized mainly due to its rarity and the inability to predict its behavior and therefore the prognosis." Treatment options range from supportive care to medical therapy to resection and, if the patient has unresectable disease, liver transplantation. However, Mehrabi and colleagues (2006) noted that "because of the rarity of this tumor and its unpredictable natural history, it is impossible to assess the effectiveness of these respective therapies." In their review from 2010, Grossman and Millis stated that the rarity of the tumor "limits the amount of current and relevant data available for analysis" with regards to treatment options.

Liver resection is the treatment of choice; however less than 10% of patients are resection candidates due to the predominantly multifocal or diffuse nature of the tumor. Unfortunately, in cases where extensive liver resection was performed for patients with widespread liver tumor, aggressive recurrence of tumor as well as fulminant hepatic failure has been reported (Mehrabi, 2006).

In our review of the evidence published over the past 10 years, we found three retrospective analyses. Mehrabi (2006) reviewed the literature and reported a 5-year survival rate of 54.5% for patients who received a liver transplantation. However, the widely varying quality and quantity of information that the authors could glean from each article, which resulted in significant gaps in the reporting of the evidence, introduces uncertainty as to important patient characteristics such as the demographic profile of the patients, the extent of disease and the reason for liver transplantation.

In the remaining evidence that we reviewed, we found a reported 1-year patient survival rate of 81 - 93% and a reported 5-year survival rate of 67 - 83%. Each of the two analyses in which these survival rates were found has limitations that can impact the results. In Lerut (2007), almost 20% of the questionnaires that were used to collect data lacked a response to a significant percentage of questions. In addition, before transplantation 30% of patients received highly various combinations of therapies. In Rodriguez (2008), the duration of patient follow-up for a significant number of patients was considerably shorter than 5 years, weakening confidence in generalizability.

The evidence does not include a large number of Medicare-aged patients. It is not possible to determine the age range for the patients who received liver transplantation in the Mehrabi (2006) article. The age range in the Lerut (2007) article was 4 - 65 years and in the Rodriguez (2008) analysis the age range was 0 - 70 years but the number and percentage of patients 65 years old and older were not reported. In addition, Lerut and colleagues (2007) did not report the survival rate separately for those 65 years old and older. The effect of comorbidities on survivorship is unclear.

Another limitation is the paucity of reported outcomes concerning quality of life. Lerut (2007) reported an increase (i.e., an improvement in the patient's performance status) in the median Karnofsky score however the pretransplant range of scores was extremely variable. Also, the pretransplant median score was 90, which indicates a high performance status. Since a good percentage of patients were highly functional prior to transplant, the usefulness of the change in score is uncertain. Without the ability to follow changes to individual patient scores as with a longitudinal analysis, it is unclear if a significant improvement occurred. Finally, the authors do not state whether the Karnofsky score is an accepted, validated measurement tool for quality of life outcomes in this particular patient population.

During our review we found only one guideline that addressed the use of liver transplantation for patients with HAE. The 2005 AASLD guideline noted that "transplantation is uncommonly required" however transplantation is not necessarily contraindicated for patients with large tumors. AASLD acknowledged that this recommendation was based upon opinion and descriptive epidemiology rather than evidence from clinical studies. Also, NCCN does not have a clinical practice guideline that addresses HAE. Finally, we note that OPTN has not implemented a MELD exception for HAE for allocation purposes.

Upon review of the available evidence which has accumulated since the 2002 NCD, we believe that the evidence base does not support a broad national coverage decision, mainly due to the significant imprecision about estimates of benefit and harm. It is not apparent at this time that the available evidence clearly and broadly distinguishes patients who will experience an improved outcome from those who will derive harm such as postoperative complications or adverse effects from the life-long immunosuppressive medication that is necessary after transplantation. There are inherent challenges in developing durable conclusions about a complex surgical procedure as liver transplantation for such rare malignancies when there are no randomized clinical trials.

It is also daunting to create a general profile of a clinically appropriate patient in the use of liver transplantation in HAE. Though technical factors and underlying patient physiology would be expected to vary little among geographic regions, the practice of medicine with regards to organ transplantation reflects the need to reasonably account for distinctions based on patent selection, transplant centers and their surgical staff. Moreover, we recognize the need for timely judgment and decisions for transplantation for these lethal and complex rare end stage liver diseases. In this aggressively lethal disease, this treatment may offer the only relief. It is unclear which patients could benefit in this rare disease, but some patients do appear to benefit. Therefore, Medicare coverage of this treatment may be best considered only in carefully selected patients on a case by case basis at this time.

Disparities

Gender and ethnic/racial groups appear to be adequately represented in liver transplantation. Based on OPTN data from February 17, 2012, of the 5,614 liver transplants performed in 2011, whites received 3,852 of the liver transplants while other groups received 1,762 transplants. Hispanics account for 28% (814 of 2,882) of the liver transplant patients on the wait list and African Americans account for 50% (617 of the 1,217) liver transplant patients on the waitlist. Likewise, genders are adequately represented on the wait list, with females proportionately represented relative to the incidences of the malignancies, which occur predominantly in males. Based on 2011 OPTN data, there are 419 males and 116 females on the transplant wait list for liver cancers. There were 2,046 female recipients (35% of the total 5,840 patients) of liver transplants performed for all indications (OPTN, 2012). We could not find any overall gender and ethnic/racial data for liver transplant in CCA, HAE, or NETs; therefore we could not draw any conclusions.

These malignancies are generally lethal, and transplantation is typically a treatment of last resort. The apparent criteria for transplantation for these rare malignancies are (1) the patient is not a liver resection candidate and (2) the patient is carefully selected. OPTN liver allocation policies include language related to resection candidates and tumor assessments, which are based on individual medical judgments with respect to each patient. Beyond these materials, the available evidence reflects the need carefully select patient, though there is a lack of a defined patient profile. Upon review of the available evidence, we believe that the evidence base does not support a broad positive national coverage decision regarding liver transplantation for the treatment of CCA, NET and HAE.

The infrastructure in place through the OPTN (which uses MELD scores) was put in place to ensure appropriate clinical use of transplantation and as well as appropriate liver allocation. The ongoing reporting requirements and data collection provide follow-up of survival outcomes. Data are stratified by facility and the OPTN reviews its criteria and MELD score to update them in accordance with clinical advances.

Summary

In summary, we conclude that the initial determinations of coverage of liver transplantation in patients with these three rare malignancies should be determined by our local administrative contractors, who are in a better position to consider characteristics of individual beneficiaries and the performance of transplant centers within their jurisdictions.

1. We recognize the presence of evidence regarding the use of liver transplantation in patients with CCA, HAE, and NETs but believe its limitations present impediments to broad positive national coverage.
2. Many limitations of the evidence base arise from the rarity of these malignancies.
3. We are mindful of the poor survival outcome with alternative nonsurgical therapies for this particular patient population. We recognize that the beneficiaries' ability to attain improved health outcomes is maximized when liver transplantation is furnished in settings that have appropriately trained, experienced operators in the context of a multidisciplinary team in a setting that assures sufficient volume to maintain proficiency. This assures certain protections are in place to enhance the likelihood of benefit.
4. We believe there is some evidence to demonstrate that liver transplantation may, within the confines of a specifically designed protocol, provide improved outcomes in carefully selected patients.

5. This will, in conjunction with the established transplant OPTN infrastructure, maximize the opportunity for optimal outcomes based on the contractor's ability to scrutinize individual patient characteristics and apply sound medical judgment on a case-by-case basis.
6. Given the need to make critically time sensitive evaluations and decisions, we defer to the ability of our local contractors. We believe that Medicare coverage under local contractor discretion balances these considerations in the interests of our beneficiaries.

IX. Conclusion

The available evidence does not clearly and broadly distinguish the patients who will experience an improved outcome from those who will derive harm such as postoperative complications or adverse effects from the life-long immunosuppressive medication that is necessary after transplantation. However, taking into consideration the rarity and lethality of the condition, the possibility of benefit in highly selected patients in specialized cancer transplant centers and the application of the OPTN parameters for the organ waitlist and allocation, we believe that local Medicare contractor determination on a case-by-case basis balances these considerations in the interests of our beneficiaries. Our local contractors are in a better position to consider characteristics of individual beneficiaries and the performance of transplant centers within their jurisdictions.

Therefore we are revising section 260.1 of the Medicare National Coverage Determinations Manual. Under the revised policy, Medicare Administrative Contractors acting within their respective jurisdictions will make an initial determination of coverage under section 1862(a)(1)(A) for adult liver transplantation in beneficiaries with the following malignancies: (1) extrahepatic unresectable cholangiocarcinoma (CCA) (2) liver metastases due to a neuroendocrine tumor (NET) and (3) hemangioendothelioma (HAE).

General Methodological Principles of Study Design
(Section VI of the Decision Memorandum)

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of an illness or injury or to improve the functioning of a malformed body member. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to help ensure adequate numbers of patients are enrolled to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study’s variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. We are interested in the results of changed patient management not just altered management. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. For most determinations, CMS evaluates whether reported benefits translate into improved health outcomes. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

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